COMPOSITION

FIELD OF THE INVENTION

The present invention relates to therapeutic compositions and in particular compositions including honey or honey derivatives.

BACKGROUND OF THE INVENTION

Honey has been used as a natural remedy and therapeutic aid since ancient times. The anti-microbial properties of honey have long formed part of both folk and scientific knowledge. Applications for honey have included topical application for wounds, ulcers, burns and similar conditions. Honey has also been known to be used as a demulcent for use in the gastro-intestinal tract for soothing or allaying irritation of inflamed or abraded surfaces. Therapeutic benefits of honey use are manifested by a reduction in inflammation, swelling and pain; prevention and control of infection in a wound; reduction in malodour and exudate; assisted debriding of wounds and improved granulation and epilthelialisation of new tissue. These advantages help promote the rapid healing of a wound with minimal scarring.

Whilst these properties encourage the use of honey as a wound healing agent and provide a moist wound environment, regarded as beneficial to the healing of wounds, use has been mainly restricted to unadulterated honey which has been applied in various forms of wound dressings and treatments. Application of honey directly presents difficulties arising from some inherent properties of the material. Due to its relatively low viscosity and fluid nature, plus natural "stickiness", honey tends to contaminate the local environment around a treatment region. The disadvantage of direct honey use is accentuated by the fact that honey at body temperature becomes reasonably fluid and migrates from a treatment site to further increase the chance of transfer to unintended areas. Use of honey can be

time consuming, messy and impractical.

Attempts have been made to address at least some of these problems by the use of wound dressings which may form a physical barrier to honey migration and which may also be impregnated with honey. The use of these methods has added an extra layer of expense to treatment with honey and has provided variable success.

In using honey, the presence of wound fluid or exudate also dilutes the therapeutic agent exacerbating the problem of diminished contact time with the wound and diminished therapeutic efficacy. Attempts have also been made to address at least some of these problems by combination with other ingredients. Again the outcome has been variable in success rate. It is preferred, and in some cases, essential, that any combination be sterilised prior to use or commercial distribution. One common form of sterilisation requires gamma irradiation at a dose level that is toxic to microorganisms. Such a process is known to cause breakdown or undesirable changes in the matrix of a honey admixture.

While the therapeutic properties of honey are recognised and appreciated, there remain problems with the practicality of using honey on wounds.

SUMMARY OF THE INVENTION

Throughout this specification, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element or integer or group of elements or integers but not the exclusion of any other element or integer or group of elements or integers.

In one form although it need not be the only or indeed the broadest form the invention resides in a composition comprising:

honey or a honey derivative;
a fatty ester, wax or wax-like compound; and
a surfactant.

The honey may be a single type of honey or may be a combination of one or more honeys. The one or more honeys may be selected for therapeutic properties which may include anti microbial activities. The honeys may be substantially derived from the flowers of one or more *Leptospermum* species. In one embodiment, a honey derivative may be used. A honey derivative may be a modified form of honey formed by any one of various processes known to a skilled addressee. The honey derivative may include a modified honey where one or more components have been fully or partially removed. The honey or modified honey may have components added to it or treated in a manner to improve its functionality. It may be a composition of compounds formulated in a manner to have a similar functionality as honey yet contain little or no honey. In the International Honey Industry, honey derivative is often applied to a product that is totally or substantially artificial honey and is sold as a honey substitute. These substances are known to a person skilled in the art.

Combinations of honey may include at least one honey with peroxide associated antibacterial activity and at least one other honey with non peroxide associated antibacterial activity. The honey or honeys may be selected on the basis of natural sugar levels to regulate natural crystal formation. The honeys may also be selected on the levels of physiologically active compounds including but not limited to flavonoids, alkaloids, growth regulators and compounds that cause stimulation of TNF-alpha release.

Honey is preferably present as at least 50% of the composition. Preferably the honey is present in the range of 70-90% of the composition and most preferably is present in a concentration at or around 80% of the composition. The percentage compositions in this specification are calculated on percentage weight/weight (%

wt/wt).

The fatty ester, wax or wax-like compound preferably has a narrow melting point range around 40°C. Preferably the wax or wax like material has a melting point of 45°C or less. The wax like material may be Myristyl Myristate. Alternatively or additionally, the wax or wax like material may be an emollient fatty ester or fatty alcohol. The Myristyl Myristate may be Crodamol MM.

The fatty ester, wax or wax-like compound may be present in the range of 1-50% of the composition. Most preferably the fatty ester or wax or wax-like compound is present in the range of 10-30%. In a preferred embodiment the fatty ester, wax or wax-like compound is present at or around 15% of the ointment.

The surfactant may be a low irritant, mild non ionic surfactant. The surfactant may be ethoxylated almond oil, preferably ethoxylated sweet almond oil. The surfactant may alternatively comprise or include ethoxylated caster oil or ethoxylated evening primrose oil. The surfactant may be Crovol A70. The surfactant may be present in the range of 2-10%. Preferably the surfactant is present in the range of 2-7%. Most preferably the surfactant is present at or around 5% of the composition.

In a further aspect the invention resides in a method of producing a therapeutic honey ointment, the method comprising the steps of:

heating honey to a temperature which is below a temperature that will cause degradation, complete or partial, of one or more functional enzymes in honey;

combining a wax and a surfactant by heating and mixing;

cooling the mixture of wax and surfactant until the mixture has a temperature similar to the temperature of the honey; and

combining the honey with the wax and surfactant.

"Wax" in this context includes fatty esters and wax-like compounds.

The one or more functional enzymes in honey may be glucose oxidase. The maximum temperature of the heated honey may be 45°C.

The wax and surfactant mixture may be heated to a temperature in the range of 50-60°C.

The wax and surfactant mixture may be mixed through the honey with high shear mixing until homogeneous, preferably avoiding overheating of the mixture.

The method may include the step of sterilising the ointment. The ointment can be sterilised by applying one or more doses of gamma irradiation. The gamma irradiation may be provided at levels between 25-35kGy.

The expression "ointment" in this specification may be understood to extend to any suitable physical state including, but not restricted to a gel, a paste, a cream, a lotion, a balm and a salve.

The method may further include the step of impregnating a bandage or dressing with the ointment for use on a subject.

The method may further include the step of packaging the ointment for distribution.

In a further aspect the invention extends to a method of treating a subject by applying one or more doses of an ointment made according to the above method or comprising the above described ingredients.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to an easy to use, effective and stable honey

based composition preferably presented as an ointment. The ointment may be formed from a combination of honey or honey derivative, a surfactant and a wax or wax-like component or fatty ester.

The honey component of the ointment may include a combination of one or more honeys selected for their therapeutic properties. The honeys may be derived from the Australian or New Zealand *Leptospermum* species. The honeys may include a combination of two or more honeys selected for differing but preferably complementary physiological/therapeutic action including those with peroxide and non peroxide antibacterial activity. This combination may ensure a broad spectrum of antibacterial activity. There are many known types of honey. Many are identified in publications such as *Honey and Pollen Flora, Clemson A, INKATA PRESS Pty Ltd, Melbourne, 1985* and similar reference works. Honeys may be selected on the basis of the presence of flavonoids which may act as an anti-oxidant resulting in inflammation reduction. Honeys may also be selected for the presence of growth factors which can assist with granulation, epithelialisation and the growth of new tissue to ensure a progressive and satisfactory healing process. The honeys may also be selected on the presence of or levels of physiologically active compounds including but not limited to flavonoids, alkaloids, growth regulators and compounds that cause stimulation of TNF-alpha release.

The surfactant is preferably a low irritant, mild chemical. Preferably the surfactant is non ionic as, in general, this class of compounds is milder than ionic surfactants. A preferred surfactant is an ethoxylated triglyceride and in particular sweet almond oil or a derivative thereof. Alternatively it is possible to substitute ethoxylated castor oil or ethoxylated evening primrose oil, preferably in non ionic form.

An example of a commercially available product is CROVOL A70 which is derived from sweet almond oil in an ethoxylated form. The international nomenclature for cosmetic ingredients has allotted the name of PEG-60 almond glycerides to CROVOL A70. This product is a long chain ethoxylate and has been shown to

have a very low tendency to irritation. CROVOL A70 has a chemical description as ethoxylated (70% by weight) sweet almond oil (CAS 124046-50-0) and may be obtained from Croda Australia, Villawood, Sydney.

An additional ingredient is a fatty ester, wax or wax-like compound. Preferably the fatty ester or wax has a relatively narrow melting range around 40°C and preferably in the range of 37-43°C. The preferred melting point is selected so that the ointment is substantially non-running at the body temperature of a patient which is usually around 37°C in a person but may be higher in domestic animals. In general however, the invention is suitable for both veterinary and human use. One means of assessing whether the ointment is non-running is to place a sample on a slope, preferably at 45°, and demonstrate that the sample does not freely flow down the incline at 25°C.

A preferred wax is Myristyl Myristate (CAS 3234-85-3). This is a wax with a low melting point, usually in the range of 37-43°C. It has good skin softening and lubricating properties. Alternative ingredients may include any emollient fatty ester or fatty alcohol that satisfies the condition of having a relatively narrow melting range around 40°C. This temperature is above normal body temperature but it is also below the denaturing temperature of functional enzymes in honey which is generally accepted to be around 45°C. Most fatty esters have long hydro-carbon chains that are very stable. The ester group at the end of the molecule also provides a stable and non-reactive aspect to the compound, making it safe to use for this application.

An example of a commercially available source of Myristyl Myristate is Crodamol MM which is available from Croda Australia, Villawood, Sydney.

In a preferred method of manufacture, honey is heated to a temperature that will not degrade the functional enzymes, such as glucose oxidase, which occur in honey. Preferably this temperature is a maximum of 45°C. Separately, the wax

and surfactant are heated while being mixed until both are fully melted. The temperature in this process may reach between 50-60°C. The wax/surfactant mixture is allowed to cool to the temperature of the honey at which time it is added to the honey with high shear mixing until homogenous. The mixing period may be relatively brief. It is preferred to avoid heating honey above the upper identified temperature as such a process may lead to degradation of functional enzymes with resulting diminution of therapeutic effect.

The mixed ointment may then be allowed to cool and be packaged for distribution.

Preferably the ointment is also sterilised particularly to remove or reduce *Clostridium sp* spores and to provide an associated reduction in bioburden levels. The preferred method of sterilisation is through the use of gamma irradiation, preferably at levels between 25-35kGy. One of the benefits of the present ointment is that it remains substantially stable and homogenous after irradiation at these levels. The current formulation may be described as a fine wax dispersion in a honey matrix. Without wishing to be tied to any one theory, it appears the surfactant acts to keep the wax particles small and enables them to be suspended and dispersed throughout the honey. It has been found that some emulsifiers including lanolin are prone to denaturing or breakdown under irradiation making them unsuitable for use in the present composition.

The ointment may be formulated according to the following proportions:

Ingredient	Range (%wt/wt)
Honey or honey derivative	50 –97%
Myristyl Myristate	1-50%
Ethoxylated sweet almond oil	2-15%

Preferably honey is present in the range of 75-84%. Myristyl Myristate may be the range of 15-20% and ethoxylated sweet almond oil may be present in the range of

1-7%.

The preferred embodiment has a composition of honey 80%, Myristyl Myristate 15% and ethoxylated sweet almond oil 5%.

It is envisaged that the present ointment may also be used for cosmetic rather than therapeutic purposes. In this case, selection of honeys with therapeutic characteristics is not essential. Honeys may be selected for cosmetic benefits such as providing a general moisturising action. Clearly, honeys may also be selected for the treatment of essentially aesthetic problems such as comedones or pimples. Selected honeys in these cases may be bacteriostatic.

Once produced, the ointment may be packaged and distributed in any suitable fashion. It may be dispensed into tubes. Alternatively it may be formed as part of a wound dressing by impregnation into a wound dressing material. The ointment may be packed into individual screw top containers or it may be delivered in sealed capsules or sachets for single use dispensing and treatment.

The ointment of the present invention may be applied in a wide range of situations and as already noted may be used in both human and veterinary medicine, as well as for human cosmetics. In its simplest form, the ointment may be applied topically to a lesion. The frequency of application may be varied to reflect the severity of the condition and the efficacy of the treatment. It is envisaged that an application rate of up to two to three times daily may be of benefit in some circumstances while application every 2-14 days may be suitable in other circumstances where the contact time is prolonged. The ointment is preferably of suitable viscosity that it may be dispensed or molded or pressed into shape using finger pressure to adopt a configuration suitable for a lesion. That shape may be retained while the ointment is fixed in position by a support bandage or similar.

The ointment may be beneficially utilised in post surgical wounds, sinus wounds,

fistulae, burns, donor sites, infected wounds, pressure ulcers, venous ulcers, diabetic ulcers, trauma injuries, catheter exit sites, dental extraction sockets, fungating/malignant wounds, lesions, ophthalmology and surgical procedures. This list is not comprehensive. Viscosity may be selected so that the ointment is suitable for filling wound cavities. Some advantages of the composition will be demonstrated in the following non-limiting Examples.

EXAMPLE 1

Honey ointment according to the present invention was used to treat burns in paediatric patients. The ointment demonstrated an ability to deslough the wound, reduce the bacterial load and assist healing. One child had a deep partial thickness burn to the scalp that had become infected and a hard crusty eschar had formed over the wound. The honey ointment desloughed the wound, cleared the infection and the wound healed without the need for surgical debridement within five days. Another case involved a deep partial thickness burn on a child, that had become infected with bacteria that were resistant to other topical antibacterial products and oral antibiotics. After application of the honey ointment to the burn, the bacterial load was reduced within five days, allowing for successful skin grafting. The honey ointment was easy to apply to gauze dressings, which were then applied to the wounds. The honey ointment washed off easily in a shower. Dressings were changed daily over the period of treatment.

EXAMPLE 2

The honey ointment was tested in a microbiological laboratory against various bacterial organisms, including *Pseudomonas sp* isolated from wounds and resistant to antibiotics and other antibacterial products including silver sulfadiazine and povidone-iodine. The honey ointment proved very effective against all tested organisms.

EXAMPLE 3

Malodour associated with fungating tumours was reduced with the use of the honey ointment. The honey ointment was applied directly to a melolin dressing which was then applied to a fungating tumour external to the mouth cavity, which had become malodorous. Malodour was reduced within two days. The honey ointment was easy to apply and stayed in place on the wound.

EXAMPLE 4

Leg ulcers and skin tears are well suited to application of the honey ointment. One male patient with poor circulation and a difficult-to-heal leg ulcer infected with *Pseudomonas sp* and *Staphylococcus sp* was treated with honey ointment of the present invention. He had previously been on antibiotics, but as these had not helped clear the infection, he was taken off his oral antibiotics and the honey ointment was used. The honey ointment was applied directly to the wound then covered with either plain gauze or paraffin-impregnated gauze. The dressings were changed daily initially then when the wound was clean, dressings were changed every second day. The honey ointment cleared the infection and the wound was rendered clean and healing. Another male patient had a skin tear that was progressing towards an ulcerous condition and was treated with the honey ointment as described above. The wound healed within two weeks. Other ulcers and skin tears have also been treated successfully with the honey ointment.

EXAMPLE 5

A sacral area ulcer and an infected stump wound resulting from surgery were healed with the use of the honey ointment applied to a dry dressing (Combine™).

EXAMPLE 6

The honey ointment was applied directly to a partial amputation of the foot using a sterile tongue depressor and covered with a dry dressing (Combine™). The wound had been treated with pure honey but the patient had been complaining of leakage from the dressing. The treatment was changed to daily honey ointment dressings and the patient had no further complaints. Healing of the wound was subsequently uneventful.

A small and deep arterial leg ulcer infected with Methicillin-resistant *Staphylococcus aureus* (MRSA) was healed with the use of the honey ointment. Daily dressings of the honey ointment applied to a dry dressing (Combine™) helped clear the infection and heal the wound.

As a result of prior wound management, a sacral wound on a patient had macerated edges and no granulation at the base of wound. A zinc-based cream was applied around the edges of the wound and the honey ointment was applied to the wound and covered with dry dressings (Combine™) and paraffin-based dressing (Adaptic™) and followed by a film dressing (Opsite™). Dressings were changed daily. Improved granulation of the wound bed was observed, the wound edges improved and the wound size decreased until the patient was sent to another clinical site.

EXAMPLE 7

The honey ointment has also been used to help reduce caesarean section scars. The honey ointment was applied directly to the week-old scar with no dressings required.

EXAMPLE 8

Diabetic wounds have also healed with the use of the honey ointment. The honey ointment was found to be easier to apply to these wounds than pure honey and the healing response was the same as or better than pure honey dressings.

The present ointment may be applied to mucous membranes and may be dispensed into bodily cavities for the treatment of mucous membranes. The ointment may be ingested for beneficial results in some circumstances. The composition of the ointment may be such that at body temperature, compared to room or storage temperature, it will soften and conform to a wound and surface to which it is applied and will remain in place for temperatures up to 37° and preferably up to 40°.

The present invention provides real benefits in the therapeutic use of honey. The use of 100% honey is, as noted above, somewhat problematic. Additionally the use of honey in known methods can be quite irritating particularly to sensitive wounds. The present invention incorporates ingredients which may be of natural origin and which do not have marked side effects such as may arise with mineral based products. The viscosity of the invention is such that it can be easily applied to a wide range of wounds some of which are painful to touch. As the surfactant can be a water soluble, vegetable derived emollient, the ointment can be easily washed off the body and can be irrigated out of body cavities. This advantage is of considerable significance as it provides easy clean-up of both patient and surrounding environments.

Manufacture of the ointment as described provides a product which can slowly dissolve over time in body fluid rather than be subject to immediate dilution and displacement by wound exudate. Additionally the ointment may be suitable for internal use and for effective gamma irradiation sterilisation. The nature of the

product makes it practical for bulk manufacture and relatively easy dispensing into packages and containers.

The ingredients of the combination are known to be stable, inert, non irritating and safe to use in therapeutic applications. Further the composition is such that a stable and homogenous mix of ingredients is achieved within the manufacturing temperature restrictions. The present invention reduces the problems associated with raw honey used in the treatment of wounds which may cause stinging and sometimes painful sensations when applied to the wounds of patients. The ointment may be used for cosmetic purposes.

The honey ointment is preferably formulated with natural waxes and oils to provide a high viscosity gel that is easy to apply with good wash off characteristics when dressings are changed.

The honey ointment can be applied either directly to the wound or to the dressing. A thin absorbent dressing with a non/low adhering surface can be used to cover the honey ointment with additional absorbent secondary dressings applied as required.

The frequency of dressing changes required will depend on how rapidly the honey ointment is being diluted by exudate. Daily dressing changes are usual during the initial stages of wound healing. More frequent changes may be needed if the honey ointment is being diluted by a heavily exudating wound. When exudation is reduced, dressing changes can be less regular (2 to 3 days).

The honey present in the honey ointment will be gradually diluted by exudate and absorbed by the dressing. Waxes contained in the honey ointment will remain leaving a protective layer. These waxes can be washed away at each dressing change by rinsing with normal saline or similar products.

The honey ointment provides natural debridement of the wound through autolysis so the wound may appear deeper after the initial dressing changes.

It is within the scope of the invention to add other ingredients known to a skilled addressee for various additional characteristics.

Throughout the specification the aim has been to describe the preferred embodiments of the invention without limiting the invention to any one embodiment or specific collection of features. Those of skill in the art will therefore appreciate that, in light of the instant disclosure, various modifications and changes can be made in the particular embodiments exemplified without departing from the scope of the present invention. All such modifications and changes are intended to be included within the scope of the disclosure.